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2. Patent application number *(The Patent office will fill in this part)* — **9918559.7** — -7 AUG 1999

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Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its corporation — JP

07717135001

4 Title of the invention — **NOVEL PHARMACEUTICAL FORMULATION**

5 Name of your agent *(if you know one)*

ANDREW J TEUTEN
(SEE CONTINUATION SHEET)

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Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

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11. I/We request the grant of a patent on the basis of this application

Signature **Andrew J Teuten** **6 August 1999**

AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

Kim Allen

0181-966 5721

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Novel Pharmaceutical Formulation

The present invention relates to an aqueous nasal formulation for use in the treatment of respiratory disorders.

Aerosol formulations are commonly used as effective anti-inflammatory treatments, but have implications with environmental safety. The most commonly used propellants in such formulations were previously chlorofluorocarbon containing (or CFC) propellants, however, these are currently being phased out, following the 1987 Montreal Protocol Agreement.

Since then, safer hydrogen containing fluorocarbons have been used as propellants in aerosol formulations, but these are relatively expensive and the environmental impact of these new propellants has also been questioned.

Thus, there is a need for safe anti-inflammatory treatments such as aqueous nasal formulations. The corticosteroid beclomethasone dipropionate (9α-chloro-16β-methyl-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17, α21-dipropionate) is well known as a topical anti-inflammatory steroid and is found in aqueous nasal formulations.

Prior aqueous nasal formulations containing beclomethasone dipropionate, used in treating such indications as allergic rhinitis (such as Beconase™ AQ) have utilised beclomethasone dipropionate monohydrate in addition to the following constituents:

Anhydrous dextrose;
Avicel RC591 (Microcrystalline cellulose and carboxymethylcellulose sodium);
Phenylethyl alcohol;
Benzalkonium chloride;

Polyoxyethylene (20) sorbitan monooleate;
and purified water

Beclomethasone dipropionate monohydrate is not currently licensed in all territories of the world (notably not in Japan) and as a consequence, nasal formulations containing such a medicament cannot be marketed in such territories without substantial research effort and expense. However, there is an alternative anhydrous form of beclomethasone dipropionate, previously used in a nasal formulation (eg. Aldecin™ AQ) which contains the following constituents:

Micronised beclomethasone dipropionate anhydrate;
Avicel RC591 (Microcrystalline cellulose and carboxymethylcellulose sodium);
Glycerol;
Propylene glycol;
Polyoxyethylene (20) sorbitan monooleate;
and purified water.

However, in the absence of a sealed pressurised container, as with the propellant based delivery systems, these formulations may be prone to contamination. As a consequence, potentially harmful bacteria may contaminate the formulation and then be inhaled directly into the nasal cavity. Additionally, these formulations have also been known to cause irritancy, which is especially undesirable in respect of paediatric treatment.

Thus, according to the present invention we provide a pharmaceutical formulation which comprises an aqueous solution of carboxy methylcellulose sodium, glycerol, propylene glycol and polyoxyethylene (20) sorbitan monooleate, containing suspended therein particulate microcrystalline cellulose

and beclomethasone dipropionate anhydrate characterised in that said aqueous suspension further comprises:

Dextrose;
Phenylethyl alcohol;
Benzalkonium chloride;
Disodium hydrogen orthophosphate; and
Citric acid

The presence of dextrose, disodium hydrogen orthophosphate and citric acid is intended to overcome the irritancy problems associated with current anhydrous beclomethasone dipropionate formulations. This improvement is believed to be mediated through the dextrose acting as an isotonicity adjusting agent. Furthermore, the beclomethasone dipropionate anhydrate may be stabilised by appropriate selection of pH using disodium hydrogen orthophosphate and citric acid to act as a buffer.

In addition, phenylethylalcohol and benzalkonium chloride are present within the formulation to act as preservatives.

Dextrose is preferably used as dextrose anhydrous. Disodium hydrogen orthophosphate is preferably used as disodium hydrogen orthophosphate anhydrous. Citric acid is preferably used as citric acid monohydrate. Microcrystalline cellulose and carboxy methylcellulose sodium is preferably used as the branded product Avicel RC591 (which typically contains 87-91% microcrystalline cellulose and 9 -13% carboxy methylcellulose sodium).

Particulate beclomethasone dipropionate anhydrate will suitably be micronised and have a mean particle size less than 20μm, preferably less than 10μm, especially 1-5μm.

Particulate microcrystalline cellulose will preferably have a particle size in the range 1 to 100μm.

A pharmaceutically acceptable amount of micronised beclomethasone dipropionate anhydrate is present within the formulation, which is preferably between 0.025-0.25% (w/w), especially 0.1% (w/w). The branded product Avicel RC591 and propylene glycol are suspending agents and are desirably added in a suitable amount to achieve this function, preferably between 1-5% and 0.1-20% (w/w) respectively, especially 1.5% and 1.0% (w/w) respectively.

We believe that Avicel RC591 acts as a suspending agent by imparting thixotropic properties to the formulation, wherein the formulation may become a stable suspension upon being stirred, shaken or otherwise disturbed. We similarly believe that propylene glycol aids stabilisation of the formulation by reducing the bubbles which arise due to the presence of Avicel RC591 and benzalkonium chloride in the formulation.

Glycerol is added in a suitable amount to achieve its desired function as an excipient which reduces the solubility of beclomethasone dipropionate anhydrate in formulation; preferably the amount of glycerol will be such as to make the beclomethasone dipropionate anhydrate essentially insoluble in the formulation. An amount of glycerol which is preferably between 0.1-6% (w/w), especially 4.0% (w/w) will be suitable. The wetting agent, polyoxyethylene (20) sorbitan monooleate (typically supplied as the branded product Polysorbate 80) is desirably added in a sufficient quantity to achieve this function, preferably between 0.001-0.01% (w/w), especially 0.007% (w/w). The components disodium hydrogen orthophosphate anhydrous and citric acid monohydrate, which act as buffers, are desirably added in a suitable amount to achieve a final pH, following adjustment if necessary, of between 5 and 6, especially 5.5. Suitable concentrations of each component are 0.01-0.4% and 0.01-0.2% (w/w)

respectively, especially 0.31% and 0.2% (w/w) respectively. Dextrose anhydrous is an isotonicity adjusting agent and is added in a suitable amount to achieve isotonicity with fluids of the nasal cavity. Suitable concentrations are between 0.1 and 5% (w/w), especially 5.0% w/w. Phenylethyl alcohol and benzalkonium chloride are preservatives which are preferably added in concentrations between 0.001-1% (v/w) and 0.001-1% (w/w) respectively, especially 0.275% (v/w) and 0.02% (w/w), respectively.

Besides its very good antiallergic properties and the above mentioned reduction in irritancy, the benefits of the invention may include the following:

Surprisingly, we have found that phenylethylalcohol has preservative properties by killing Pseudomonas cepacia (now known as Burkhoderia cepacia) by a synergistic effect with benzalkonium chloride. Ps. cepacia is a bacterium which is capable of opportunistic infections such as blood poisoning and due to the bacterium being largely resistant to antibiotics, clinical treatment is complex. Results demonstrating this effect are shown in Figure 7.

A formulation of the present invention may be prepared by the manufacturing process according to the flow diagram shown in Figure 1.

A typical container suitable for a formulation of the present invention may be of the type exemplified in Figures 2 and 3. As a further aspect of the present invention we provide a container comprising a pharmaceutical formulation according to the present invention suitable for delivering it in the form of a nasal spray.

A suitable dosing regime for the formulation of the present invention would be for the patient to inhale deeply subsequent to the nasal cavity being cleared. During inhalation the formulation would be applied to one nostril while the other is

manually compressed. This procedure would then be repeated for the other nostril.

Wherein the patient is adult, two inhalations would be administered by the above procedure (100μg beclomethasone dipropionate anhydrate in total) four times each day.

Wherein the patient is a child, two inhalations would be administered by the above procedure (100μg beclomethasone dipropionate anhydrate in total) two times each day.

It will be appreciated that the above dosing regime should be adjusted according to the patient's age, body weight and/or symptom severity. However, the maximum daily dose should not exceed 16 inhalations for an adult and 8 inhalations for a child. If remission of the nasal symptoms is observed, the dose should be decreased as appropriate.

Examples of disease states in which the formulation of the present invention has potentially beneficial anti-inflammatory effects include allergies associated with the nasal cavity, more particularly allergic rhinitis.

Thus, according to a further aspect of the invention we provide a pharmaceutical formulation of the present invention for use in the treatment or prophylaxis of allergic rhinitis.

We also provide a use of a pharmaceutical formulation of the present invention in the manufacture of a medicament for the treatment or prophylaxis of allergic rhinitis.

More specifically, the formulation of the present invention may be illustrated by reference to the following example:

Example 1

A solution of propylene glycol (0.3kg) in purified water (23.6kg) is dispersed by mixing at 2000rpm for 5 mins. To this solution, dextrose anhydrate (1.5kg), phenylethyl alcohol (82.5g) and microcrystalline cellulose and carboxymethylcellulose sodium (Avicel RC591; 0.45kg) is then added separately and mixed for a further 10, 5 and 30 mins, respectively. The dispersing is then ceased and the mixture is allowed to stand for 60 mins to hydrate. Dispersion is resumed at 3000rpm for 10 mins and then re-adjusted to 2000rpm.

Anhydrous disodium hydrogen orthophosphate (93g) is added to purified water (1.8kg) and dissolved by mixing at 3000rpm for 15 mins. This solution is then mixed into the dispersing suspension for 5 mins as is a solution of citric acid, prepared by manually mixing citric acid (0.06kg) with purified water (600g).

Glycerol (1.2kg) was heated at 48°C ± 2°C and polyoxyethylene (20) sorbitan monooleate (Polysorbate 80; 2.1g) is then dissolved in the glycerol. A slurry is then formed by mixing micronised beclomethasone dipropionate anhydrate (30g) with the glycerol and polyoxyethylene (20) sorbitan monooleate solution at 4500rpm at 48°C ± 2°C for 30 mins. This slurry is then added to the dispersing suspension and mixed for 15 mins.

A solution of benzalkonium chloride (50% w/v; 11.82g) is then diluted with purified water (220g), heated to 35-40°C and then mixed with the drug suspension for 3 mins. Dispersion is then ceased, pH is adjusted to that of an optimum value, typically between 5 and 6, especially 5.5. The drug suspension is then filtered through 100 mesh filters and stored prior to filling into clean

bottles. This procedure results in the components being present in the following concentrations:

Micronised beclomethasone dipropionate anhydrate	0.1% (w/w)
Dextrose anhydrous	5.0% (w/w)
Microcrystalline cellulose and carboxymethylcellulose sodium (Avicel RC591)	1.5% (w/w)
Phenylethyl alcohol	0.275% (v/w)
Benzalkonium chloride solution 50% (w/v)	0.04% (v/w)
Glycerol	4.0% (w/w)
Propylene glycol	1.0% (w/w)
Polyoxyethylene (20) sorbitan monooleate	0.007% (w/w)
Disodium hydrogen orthophosphate anhydrous	0.31% (w/w)
Citric acid monohydrate	0.2% (w/w)
Purified water	to 100%.

Biological Data

The formulation of the present invention, Example 1 (beclomethasone dipropionate anhydrate aqueous nasal spray, hereinafter defined as BANS) which delivers 50 μg BDP in a single spray was tested in a variety of assays to deduce its effect upon nasal symptoms when compared with controls and a prior art formulation (Aldecin™ AQ).

1) Effect of BANS on TDI-induced nasal symptoms in sensitised guinea pigs.

Guinea pigs were immunised by 2 x 5 days intranasal application of 10% TDI (toluene 2, 4-diisocyanate) at intervals of 3 weeks. One or two weeks after the final sensitisation, a nasal allergy like response (sneeze, rhinorrhea, nasal obstruction) was provoked by intranasal application of 5% TDI. Drugs were

topically applied 0.5, 1 or 4 hr before the provocation (1 spray each nostril equivalent to 100 μg BDP), however, a control utilised animals sensitised with 5% TDI without drug treatment. Any nasal symptoms were then observed (eg. sneezing, rhinorrhea and nasal obstruction) and scored according to the criteria displayed in Table 1.

Table 1: Criteria used to assign a nasal symptom score for each group

Symptom	Score			
	0	1	2	3
Sneezing	Not observed	1-4	5-11	>12
Watery rhinorrhea	Dry nostril	Snivel observed, but remains within nostril	Snivel leaks from nostril and wets the nasolabial portion, but does not discharge	Snivel drops from the nose
Nasal obstruction	Not observed	Observed	-	-

The sum of the score was regarded as the nasal response of the animal and a 'mean score' value was given for the mean of the scores of each group. The results of this investigation are shown in Figure 4.

2) Effect of BANS on antigen induced nasal vascular permeability in sensitised rats.

Rats were immunised with DNP-As and the animals with 72 hr –PCA titre over x50 were used. Under the anaesthesia, the nasal cavity of the rat was perfused with saline. After the dye (4% pontamine sky blue (Brilliant blue) 5 ml/kg) was intravenously injected, the perfusate was collected for 10 min. Thereafter, the

antigen solution was perfused for 10 min followed by perfusion with saline for further 30 min. The dye concentration of the perfusate collected was determined by absorbance at 616nm. Drugs were topically applied 24hr and 1hr before the provocation (2 sprays at each time equivalent to 100μg BDP). Controls were prepared which utilised antigen challenged sensitised animals without drug treatment (control) and BANS placebo treatment (vehicle). The results of this investigation are shown in Figure 5.

3) Effect of BANS on the increase in intranasal pressure after antigen challenge in sensitised guinea pigs.

Guinea pigs were immunised with OVA by subcutaneous administration in mixture with FCA. The animals with 4 hr-PCA titre over x50 were used. Under the anaesthesia, a Y-shaped cannula was inserted into the trachea of larynx side. One end of the cannula was connected to the transducer to measure intranasal pressure and the other end to air bomb to supply contact flow of the air. After instillation of the antigen solution into the nose, intranasal pressure was measured for 28 min. Drugs were topically applied 24 hr and 1 hr before the provocation (4 sprays at each time equivalent to 200 μg BDP). Controls were prepared which utilised antigen challenged sensitised animals without drug treatment (control) and BANS placebo treatment (vehicle). The results of this investigation are shown in Figure 6.

4) Challenge test of BANS against Ps. Cepacia

Formulations corresponding to BANS and the same formulation containing only 0.02% (w/w) benzalkonium chloride as preservative (i.e. no phenylethyl alcohol) and the same formulation containing only 0.275% (v/w) phenylethylalcohol as preservative (i.e. no benzalkonium chloride) were challenged with an innoculum of Ps cepacia. The results, shown in Figure 7, demonstrate that the combined

preservative is much improved in respect of antimicrobial effectiveness relative to the two preservatives individually in this formulation.

Description of the drawings

Figure 1 contains a flow diagram to clearly describe the manufacturing process involved to produce a formulation of the present invention.

Figure 2 contains a cross section description of a suitable container for the formulation of the present invention.

Figure 3 contains a cross section diagram of a pump system (Valois VP3/50) with actuator suitable for use in a container such as that described in Figure 2.

Figure 4 compares the effect of BANS, Aldecin™ AQ and a control upon TDI-induced nasal symptoms at differing time intervals from drug administration.

Figure 5 compares the effect of BANS, Aldecin™ AQ, a vehicle and a control upon antigen induced nasal vascular permeability at a suitable time from drug administration.

Figure 6 compares the effect of BANS, Aldecin™ AQ, a vehicle and a control upon the increase in intranasal pressure from 0 to 28 minutes after antigen challenge.

Figure 7 shows the results of the challenge test of BANS and the same formulation without one of each of the two preservatives against Ps. cepacia.

Abbreviations

BANS	beclomethasone dipropionate anhydrate aqueous nasal spray (following Example 1, except where indicated)
BDP	beclomethasone dipropionate
TDI	toluene 2,4-diisocyanate
FCA	Freund complete adjuvant
PCA	Passive cutaneous anaphylaxis
DNP-As	Ascari's suum extracts conjugated with dinitrophenol (antigen)
OVA	Ovalbumin (antigen)
BKC	Benzalkonium chloride
PEA	Phenylethyl alcohol

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

Claims

1. A pharmaceutical formulation which comprises an aqueous solution of carboxy methylcellulose sodium, glycerol, propylene glycol and polyoxyethylene (20) sorbitan monooleate, containing suspended therein particulate microcrystalline cellulose and beclomethasone dipropionate anhydrate, characterised in that said aqueous suspension further comprises:

Dextrose;
Phenylethyl alcohol;
Benzalkonium chloride;
Disodium hydrogen orthophosphate; and
Citric acid.

2. A pharmaceutical formulation according to claim 1 characterised in that it is buffered to a pH of between 5 and 6.

3. A pharmaceutical formulation according to claim 1 characterised in that it is isotonic with fluids of the nasal cavity.

4. A pharmaceutical formulation according to claim 1 having a composition as follows:

Micronised beclomethasone dipropionate anhydrate	0.1% (w/w)
Dextrose anhydrous	5.0% (w/w)
Microcrystalline cellulose and carboxymethylcellulose sodium (Avicel RC591)	1.5% (w/w)
Phenylethyl alcohol	0.275% (v/w)
Benzalkonium chloride solution 50% (w/v)	0.04% (v/w)
Glycerol	4.0% (w/w)
Propylene glycol	1.0% (w/w)

Polyoxyethylene (20) sorbitan monooleate	0.007% (w/w)
Disodium hydrogen orthophosphate anhydrous	0.31% (w/w)
Citric acid monohydrate	0.2% (w/w)
Purified water	to 100%.

5. A container comprising a pharmaceutical formulation according to claim 1 suitable for delivering it in the form of a nasal spray.

6. A pharmaceutical formulation according to claim 1 for use in the treatment or prophylaxis of allergic rhinitis.

7. Use of a pharmaceutical formulation according to claim 1 in the manufacture of a medicament for the treatment or prophylaxis of allergic rhinitis.

8. A method of treatment of allergic rhinitis which comprises administering to a patient a pharmaceutically acceptable amount of a formulation according to claim 1.

9. A process for preparing a formulation according to claim 1 as herein before described by reference to the manufacturing flow diagram shown in Figure 1.

Figure 1

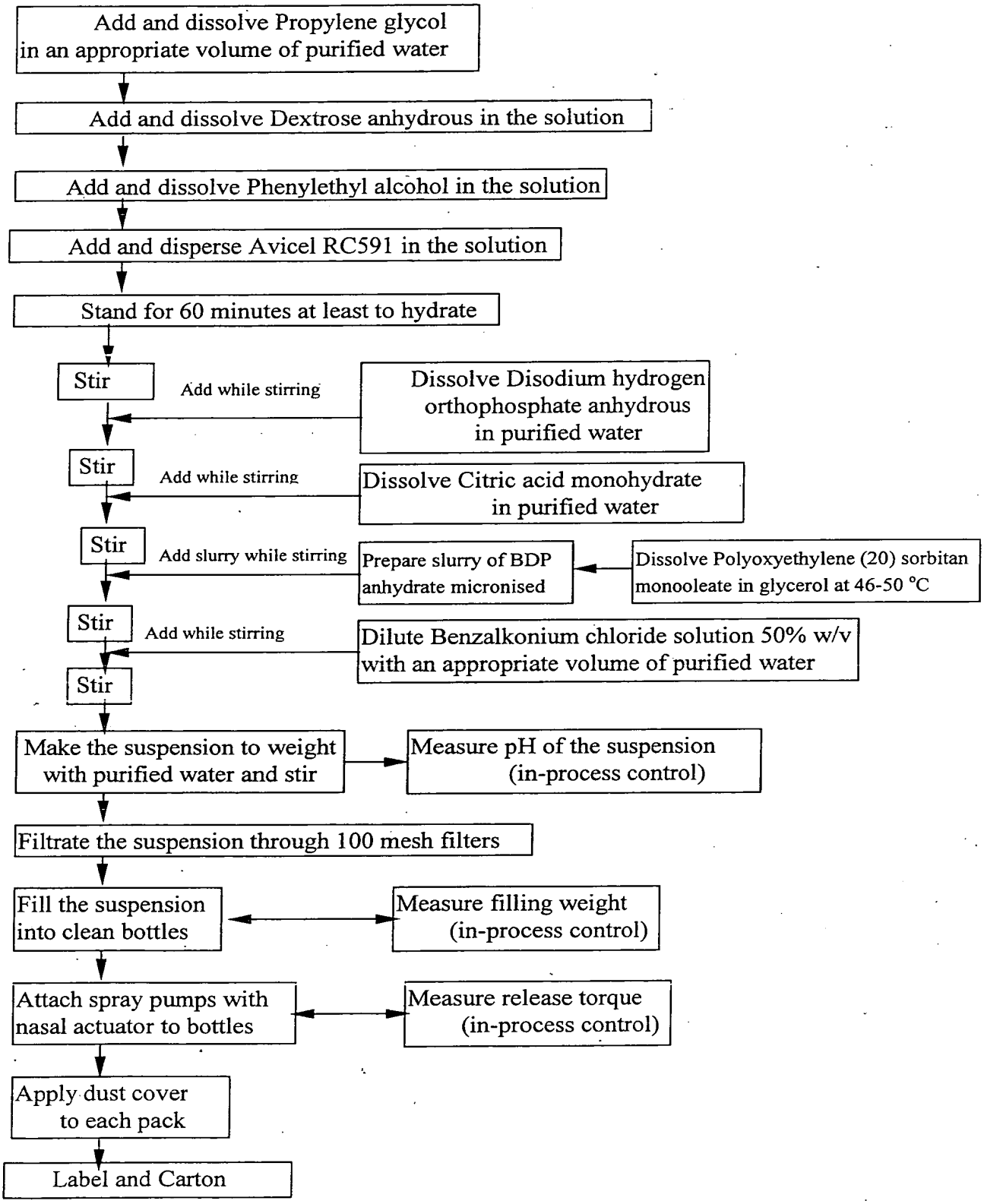

Add and dissolve Propylene glycol in an appropriate volume of purified water
Add and dissolve Dextrose anhydrous in the solution
Add and dissolve Phenylethyl alcohol in the solution
Add and disperse Avicel RC591 in the solution
Stand for 60 minutes at least to hydrate
Stir
Add while stirring
Dissolve Disodium hydrogen orthophosphate anhydrous in purified water
Stir
Add while stirring
Dissolve Citric acid monohydrate in purified water
Stir
Add slurry while stirring
Prepare slurry of BDP anhydrate micronised
Dissolve Polyoxyethylene (20) sorbitan monooleate in glycerol at 46-50 °C
Stir
Add while stirring
Dilute Benzalkonium chloride solution 50% w/v with an appropriate volume of purified water
Stir
Make the suspension to weight with purified water and stir
Measure pH of the suspension (in-process control)
Filtrate the suspension through 100 mesh filters
Fill the suspension into clean bottles
Measure filling weight (in-process control)
Attach spray pumps with nasal actuator to bottles
Measure release torque (in-process control)
Apply dust cover to each pack
Label and Carton

Figure 2

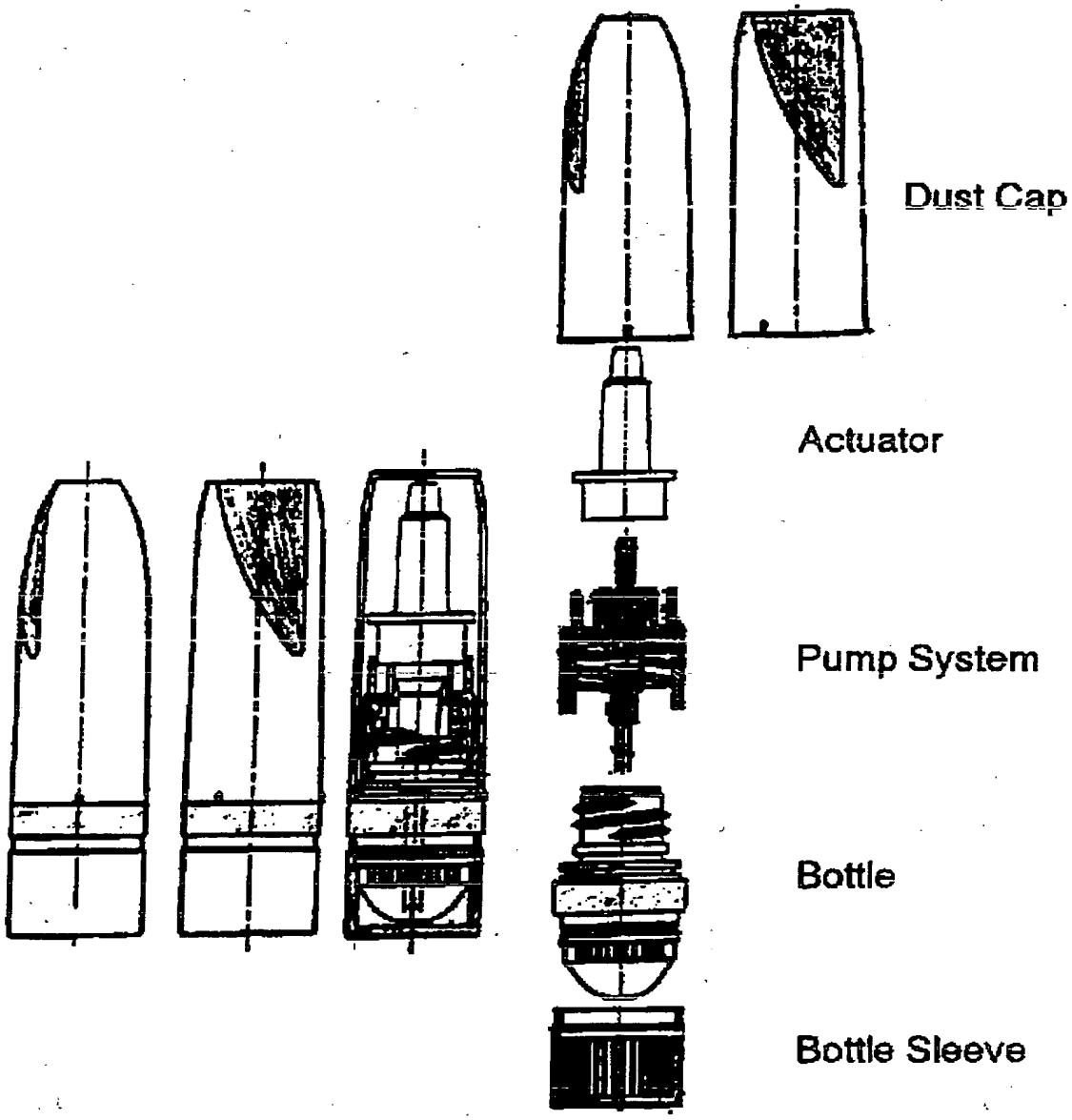


Figure 3

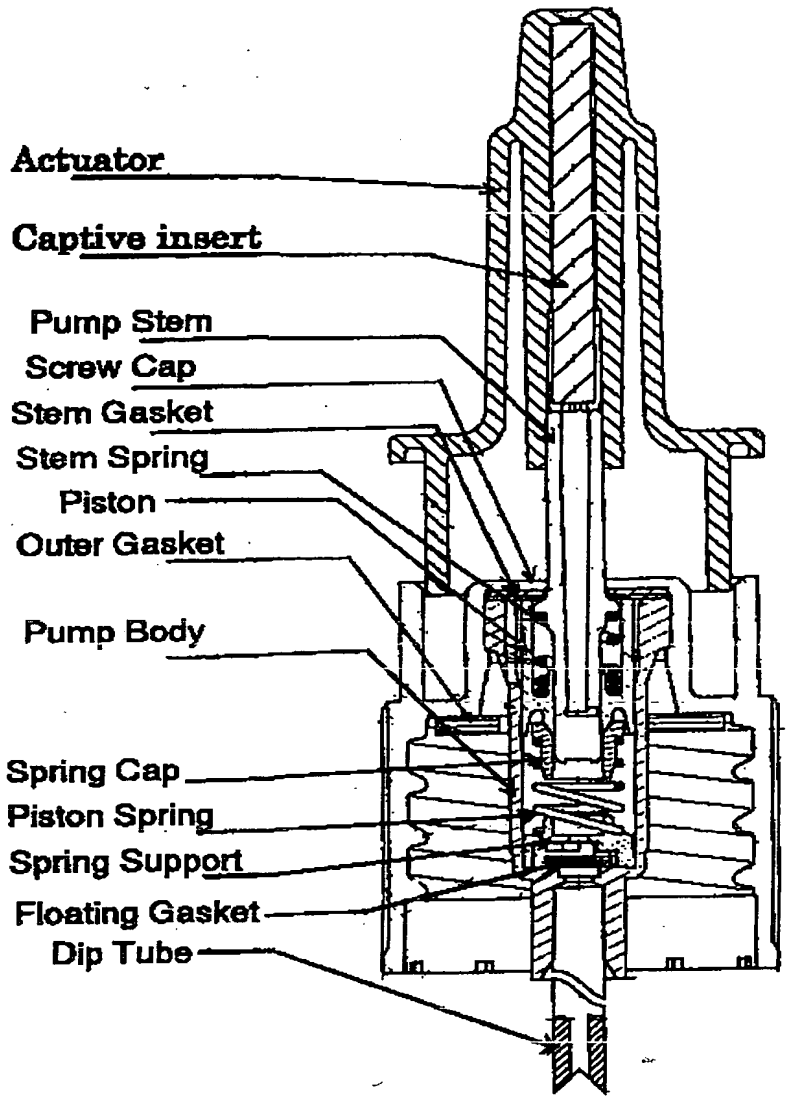

Actuator
Captive insert
Pump Stem
Screw Cap
Stem Gasket
Stem Spring
Piston
Outer Gasket
Pump Body
Spring Cap
Piston Spring
Spring Support
Floating Gasket
Dip Tube

Figure 4

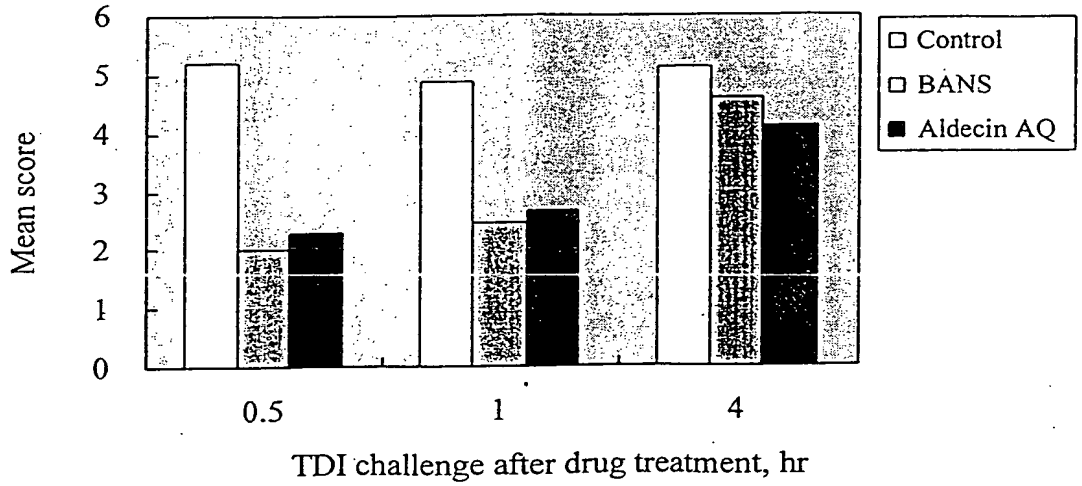
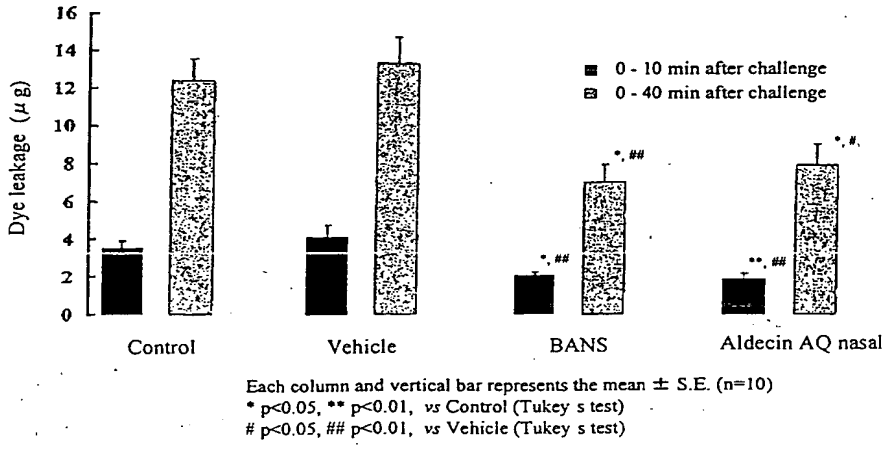
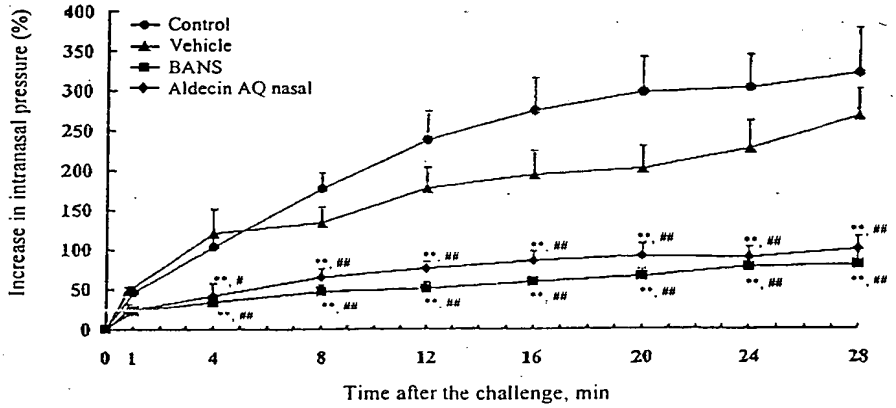


Figure 5



Each column and vertical bar represents the mean ± S.E. (n=10)
* p<0.05, ** p<0.01, *vs* Control (Tukey s test)
# p<0.05, ## p<0.01, *vs* Vehicle (Tukey s test)

Figure 6



Each point and vertical bar represents the mean ± S.E.(n=10)
* p<0.05, *vs* Control (Tukey s test)
# p<0.05, ## p<0.01, *vs* Vehicle (Tukey s test)

Figure 7

Challenge Test of BANS against Ps. cepacia

	Log_{10} reduction *				
	Log_{10} innoculum count	2days	7days	14days	28days
BKC 0.02 %w/w	6.2	0.3	1.0	1.3	1.8
PEA 0.275 %v/w	6.2	0.2	0.6	1.7	NR
BKC 0.02 %w/w + PEA 0.275 %v/w	6.2	NR	NR	NR	NR

* : Log_{10} reduction = Log_{10} (innoculum count) - Log_{10} (sample count)
NR : no recovery